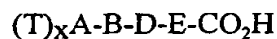


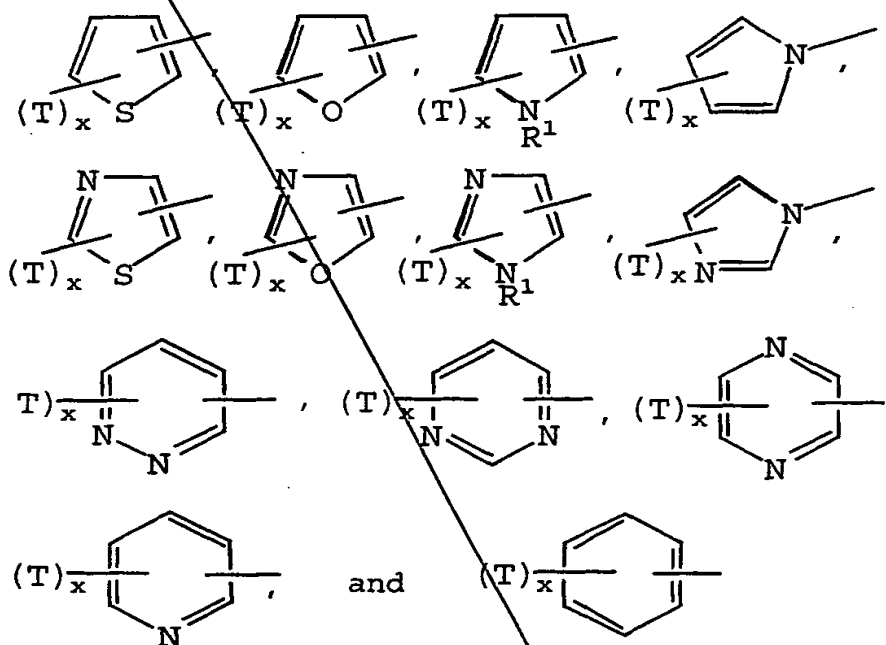
We claim:

1. Use of compounds having matrix metalloprotease inhibitory activity and the generalized formula:



wherein

- (a)  $(T)_x A$  represents a substituted or unsubstituted aromatic or hetero-aromatic moiety selected from the group consisting of:



wherein  $R^1$  represents H or alkyl of 1 - 3 carbons; and

each T represents a substituent group, independently selected from the group consisting of:

- \* the halogens -F, -Cl, -Br, and -I;
- \* alkyl of 1 - 10 carbons;

- 111 -

- Sub A'
- \* haloalkyl of 1 - 10 carbons;
  - \* haloalkoxy of 1 - 10 carbons;
  - \* alkenyl of 2 - 10 carbons;
  - \* alkynyl of 2 - 10 carbons;
  - \*  $-(CH_2)_pQ$ , wherein  
p is 0 or an integer 1 - 4,
  - \* -alkenyl-Q, wherein  
said alkenyl moiety comprises 2 - 4 carbons, and
  - \* -alkynyl-Q, wherein  
said alkynyl moiety comprises 2 - 7 carbons; and

Q is selected from the group consisting of aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, -CN, -CHO, -NO<sub>2</sub>, -CO<sub>2</sub>R<sup>2</sup>, -OCOR<sup>2</sup>, -SOR<sup>3</sup>, -SO<sub>2</sub>R<sup>3</sup>, -CON(R<sup>4</sup>)<sub>2</sub>, -SO<sub>2</sub>N(R<sup>4</sup>)<sub>2</sub>, -C(O)R<sup>2</sup>, -N(R<sup>4</sup>)<sub>2</sub>, -N(R<sup>2</sup>)COR<sup>2</sup>, -N(R<sup>2</sup>)CO<sub>2</sub>R<sup>3</sup>, -N(R<sup>2</sup>)CON(R<sup>4</sup>)<sub>2</sub>, -CHN<sub>4</sub>, -OR<sup>4</sup>, and -SR<sup>4</sup>;

wherein

R<sup>2</sup> represents H;  
alkyl of 1 - 6 carbons;  
aryl of 6 - 10 carbons;  
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; or  
arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or  
heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

- 112 -

Sub 5  
H<sup>1</sup>

R<sup>3</sup> represents alkyl of 1 - 4 carbons;  
aryl of 6 - 10 carbons;  
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; or  
arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or  
heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

10

R<sup>4</sup> represents H;  
alkyl of 1 - 12 carbons;  
aryl of 6 - 10 carbons;  
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;  
15 arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons;  
heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;  
20 alkenyl of 2 - 12 carbons;  
alkynyl of 2 - 12 carbons;  
-(C<sub>q</sub>H<sub>2q</sub>O)<sub>r</sub>R<sup>5</sup> wherein q is 1-3; r is 1 - 3; and R<sup>5</sup> is H provided q is greater than 1, or alkyl of 1 - 4 carbons, or  
25 phenyl;  
alkylenethio terminated with H, alkyl of 1-4 Carbons, or phenyl;  
alkyleneamino terminated with H, alkyl of 1-4 carbons, or phenyl;  
30 -(CH<sub>2</sub>)<sub>s</sub>X wherein s is 1 - 3 and X is halogen;  
-C(O)OR<sup>2</sup>; or

09869668 010202

-C(O)R<sup>2</sup>;

and with the provisos that a) when two R<sup>4</sup> groups are situated on a nitrogen, they may be joined by a bond to form a heterocycle, and b) unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and

x is 0, 1, or 2;

- (b) B represents a bond or an optionally substituted aromatic or hetero-aromatic ring containing 0-2 substituents T, which substituents T may independently have the meaning specified under (a), the B rings being selected from the group consisting of:

COA.T.O. 89969860

Sub  
A'

5

10



- 5 (d) E represents a chain of n carbon atoms bearing m substituents R<sup>6</sup>, wherein said R<sup>6</sup> groups are independent substituents, or constitute spiro or nonspiro rings in which a) two groups R<sup>6</sup> are joined, and taken together with the chain atom(s) to which said two R<sup>6</sup> group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group R<sup>6</sup> is joined to the chain on which said one group R<sup>6</sup> resides, and taken together with the chain atom(s) to which said R<sup>6</sup> group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring; and wherein
- 10 n is 2 or 3;  
m is an integer of 1 - 3;

each group R<sup>6</sup> is independently selected from the group consisting of:

- 15 \*
- \* fluorine;
  - \* hydroxyl, with the proviso that a single carbon may bear no more than one hydroxyl substituent
  - \* alkyl of 1 - 10 carbons;
  - \* aryl of 6 - 10 carbons;
  - 20 \* heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
  - \* arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;
  - \* heteroaryl-alkyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 8 carbons;
  - 25 \*
  - \* alkenyl of 2 - 10 carbons;
  - \* aryl-alkenyl wherein the aryl portion contains 6 - 10 carbons and the alkenyl portion contains 2 - 5 carbons;

- 116 -

Sub  
A'

5

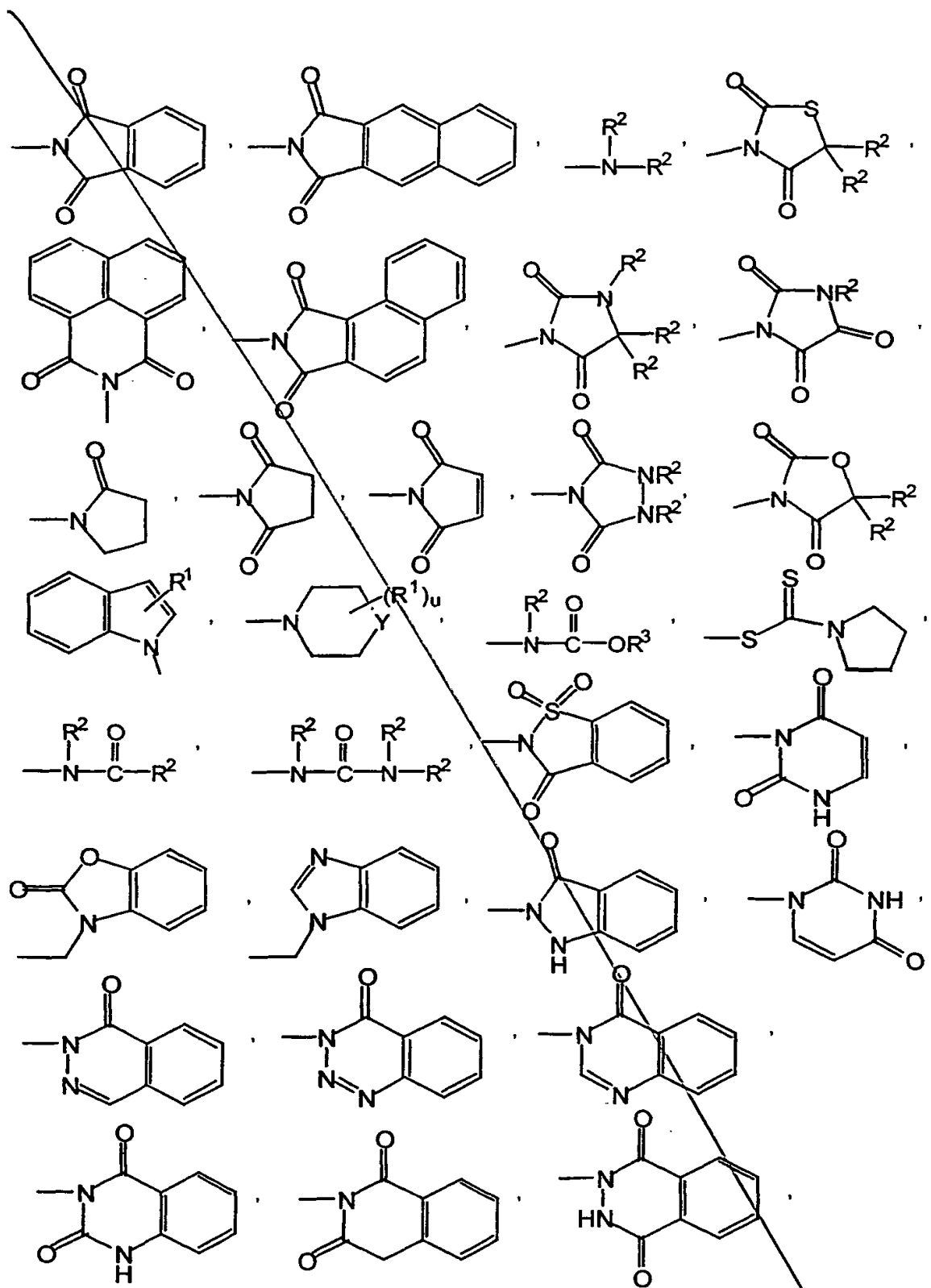
10

- \* heteroaryl-alkenyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkenyl portion contains 2 - 5 carbons;
- \* alkynyl of 2 - 10 carbons;
- \* aryl-alkynyl wherein the aryl portion contains 6 - 10 carbons and the alkynyl portion contains 2 - 5 carbons;
- \* heteroaryl-alkynyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkynyl portion contains 2 - 5 carbons;
- \*  $-(CH_2)_tR^7$  wherein  
t is 0 or an integer of 1 - 5; and  
 $R^7$  is selected from the group consisting of

09869668.010202

Sub  
A1

202010-89959850





and corresponding heteroaryl moieties in which the aryl portion of an aryl-containing  $R^7$  group comprises 4 - 9 carbons and at least one N, O, or S heteroatom;

wherein

Y represents O or S;

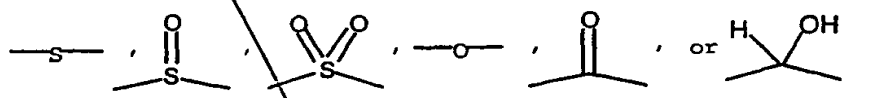
$R^1$ ,  $R^2$ , and  $R^3$  are as defined above; and

u is 0, 1, or 2; and

\*  $-(CH_2)_vZR^8$  wherein

v is 0 or an integer of 1 to 4; and

Z represents



$R^8$  is selected from the group consisting of:

alkyl of 1 to 12 carbons;

aryl of 6 to 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl wherein the aryl portion contains 6 to 12 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

$-C(O)R^9$  wherein  $R^9$  represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 -

Sub  
A1

202010 89969850

- 119 -

9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons;

and with the provisos that

- when  $R^8$  is  $-C(O)R^9$ , Z is S or O;
- when Z is O,  $R^8$  may also be  $-(C_qH_{2q}O)_rR^5$  wherein q, r, and  $R^5$  are as defined above; and

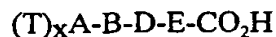
- \*  $-(CH_2)_wSiR^{10}_3$  wherein  
w is an integer of 1 to 3; and  
 $R^{10}$  represents alkyl of 1 to 2 carbons;

and with the proviso that

- aryl or heteroaryl portions of any of said T or  $R^6$  groups optionally may bear up to two substituents selected from the group consisting of  
 $-(CH_2)_yC(R^4)(R^3)OH$ ,  $-(CH_2)_yOR^4$ ,  $-(CH_2)_ySR^4$ ,  $-(CH_2)_yS(O)R^4$ ,  
 $-(CH_2)_yS(O)_2R^4$ ,  $-(CH_2)_ySO_2N(R^4)_2$ ,  $-(CH_2)_yN(R^4)_2$ ,  $-(CH_2)_yN(R^4)COR^3$ ,  
 $-OC(R^4)_2O-$  in which both oxygen atoms are connected to the aryl ring,  
 $-(CH_2)_yCOR^4$ ,  $-(CH_2)_yCON(R^4)_2$ ,  $-(CH_2)_yCO_2R^4$ ,  $-(CH_2)_yOCOR^4$ ,  
 $-halogen$ ,  $-CHO$ ,  $-CF_3$ ,  $-NO_2$ ,  $-CN$ , and  $-R^3$ , wherein  
y is 0 - 4; and  
 $R^3$  and  $R^4$  are defined as above, and any two  $R^4$  which are attached to one nitrogen may be joined to form a heterocycle;

and pharmaceutically acceptable salts and prodrugs thereof for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

2. Use of compounds according to claim 1 having matrix metalloprotease inhibitory activity and the generalized formula:



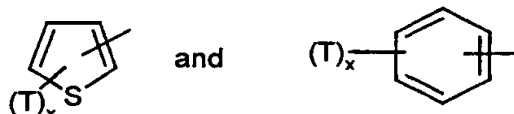
09869668-010202

Sub  
A1

- 120 -

wherein

- (a)  $(T)_x A$  represents a substituted or unsubstituted aromatic or hetero-aromatic moiety selected from the group consisting of:



wherein

each T represents a substituent group, independently selected from the group consisting of:

- \* the halogens -F, -Cl, -Br, and -I;
- \* alkyl of 1 - 10 carbons;
- \* haloalkyl of 1 - 10 carbons;
- \* alkenyl of 2 - 10 carbons;
- \* alkynyl of 2 - 10 carbons;
- \*  $-(CH_2)_p Q$ , wherein  
p is 0 or an integer 1 - 4,
- \* -alkenyl-Q, wherein  
said alkenyl moiety comprises 2 - 4 carbons, and
- \* -alkynyl-Q, wherein  
said alkynyl moiety comprises 2 - 7 carbons; and

Q is selected from the group consisting of  $-OR^4$  and  $-SR^4$ ;

wherein

$R^4$  represents H;

alkyl of 1 - 12 carbons;

aryl of 6 - 10 carbons;

202010" 89369260

50h  
A' 5

10

15

20

25

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons;

heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

$-\text{C}(\text{O})\text{OR}^2$ ; or

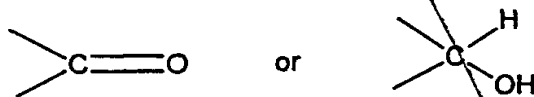
$-\text{C}(\text{O})\text{R}^2$ ;

and with the proviso that unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and

x is 0, 1, or 2;

(b) B represents an optionally substituted phenyl or thienyl ring containing 0-2 substituents T, which substituents T may independently have the meaning specified under (a).

(c) D represents



(d) E represents a chain of n carbon atoms bearing m substituents  $\text{R}^6$ , wherein said  $\text{R}^6$  groups are independent substituents, or constitute nonspiro rings in which two groups  $\text{R}^6$  are joined, and taken together with the chain atom(s) to which said two  $\text{R}^6$  group(s) are attached, and any intervening chain atoms, constitute a 5 or 6-membered ring; and wherein

Sub  
A'

5

10

15

20

25

09869666-010202

- 122 -

n is 2 or 3;

m is an integer of 1 or 2;

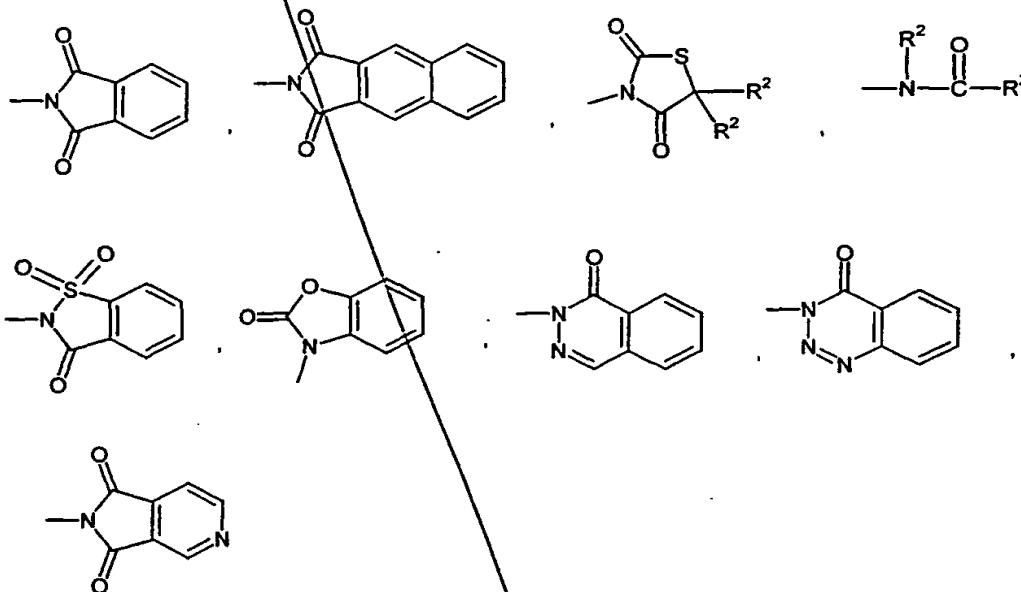
each group  $R^6$  is independently selected from the group consisting of:

\* arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;

\*  $-(CH_2)_tR^7$  wherein

t is 0 or an integer of 1 - 5; and

$R^7$  is selected from the group consisting of



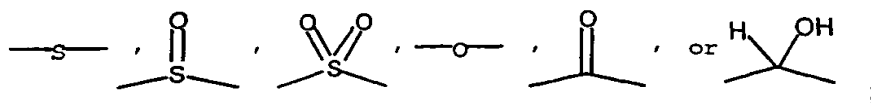
wherein

$R^2$  is independently selected from the group consisting of: H; aryl of 6-10 carbons

\*  $-(CH_2)_vZR^8$  wherein

v is 0 or an integer of 1 to 4; and

Z represents



$R^8$  is selected from the group consisting of:

alkyl of 1 to 12 carbons;

aryl of 6 to 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl wherein the aryl portion contains 6 to 12 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

$\text{---C(O)R}^9$  wherein  $R^9$  represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons;

and with the provisos that

- when  $R^8$  is  $\text{---C(O)R}^9$ , Z is S or O;
- when Z is O,  $R^8$  may also be  $\text{---(C}_q\text{H}_{2q}\text{O)}_r\text{R}^5$  wherein q, r, and  $R^5$  are as defined above; and

\*  $\text{---(CH}_2\text{)}_w\text{SiR}^{10}_3$  wherein  
w is an integer of 1 to 3; and  
 $R^{10}$  represents alkyl of 1 to 2 carbons;

and with the proviso that

202010-89969860

Sub  
A1

5

10

15

20

25

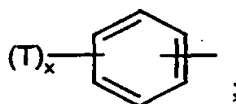
aryl or heteroaryl portions of any of said T or R<sup>6</sup> groups optionally may bear up to two substituents selected from the group consisting of OR<sup>4</sup>, N(R<sup>4</sup>)<sub>2</sub>, -OC(R<sup>4</sup>)<sub>2</sub>O- in which both oxygen atoms are connected to the aryl ring, CON(R<sup>4</sup>)<sub>2</sub>, OCOR<sup>4</sup>, -halogen, -NO<sub>2</sub>, and alkyl with up to 6 carbon atoms

wherein

R<sup>4</sup> is defined as above;

and pharmaceutically acceptable salts and prodrugs thereof for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

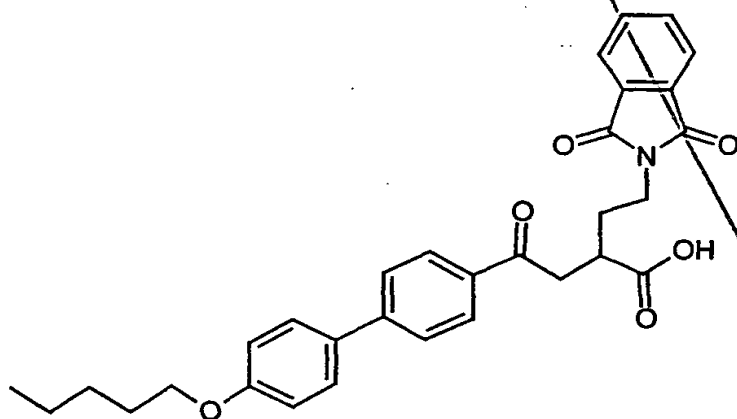
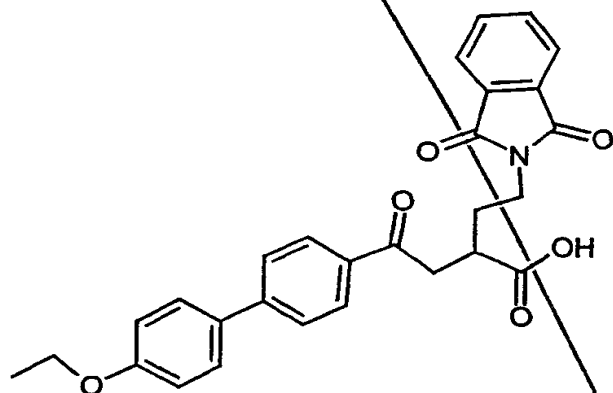
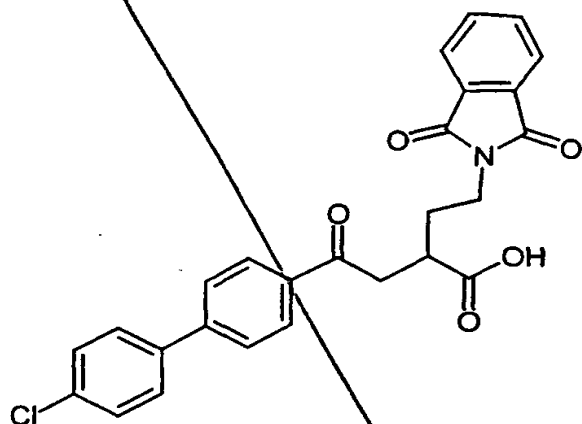
3. Use of a compound of claim 1 or 2, wherein at least one of the units A, B, T, and R<sup>6</sup> comprises a heteroaromatic ring for the manufacturing of drugs for the treatment and prevention of respiratory diseases.
4. Use of a compound of claim 1 or 2, wherein in said E unit, n is 2 and m is 1 for the manufacturing of drugs for the treatment and prevention of respiratory diseases.
5. Use of a compound of claim 1 or 2, wherein A is



B is p-phenylene and D is a carbonyl group for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

6. Use of a compound of claim 1 or 2, wherein the compound is selected from the following group:

- 125 -

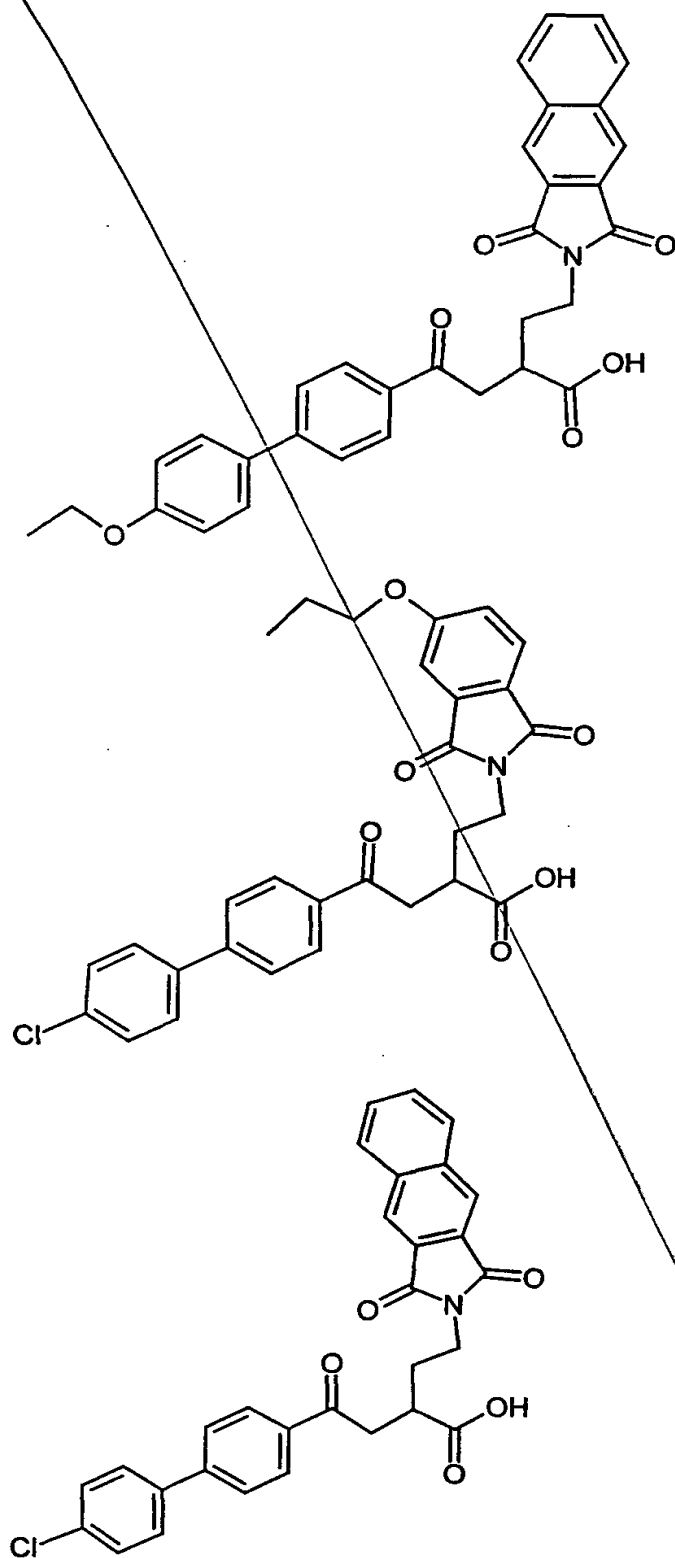
Sub  
A'



- 126 -

Sub  
A1

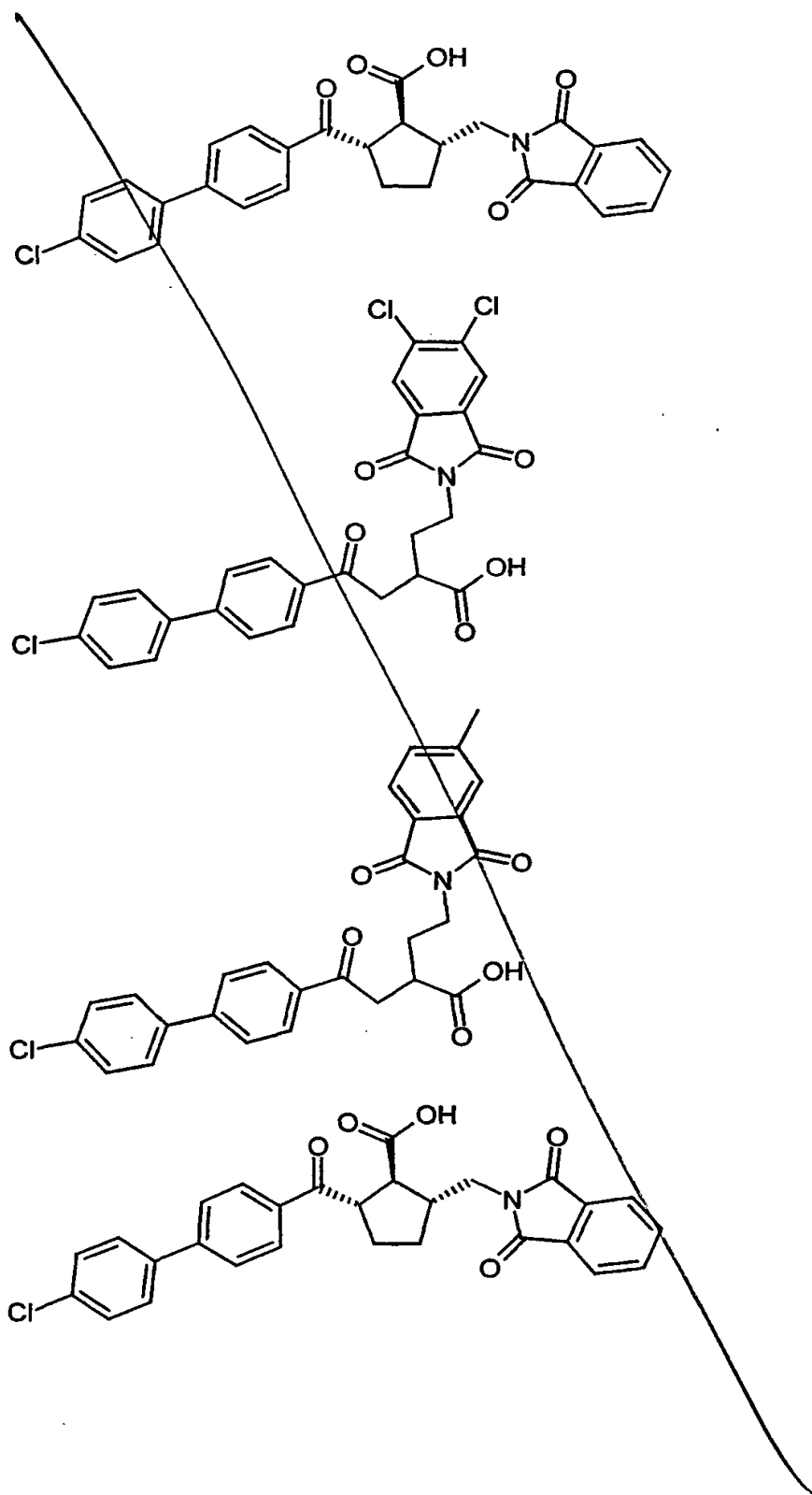
09869666-010200



- 127 -

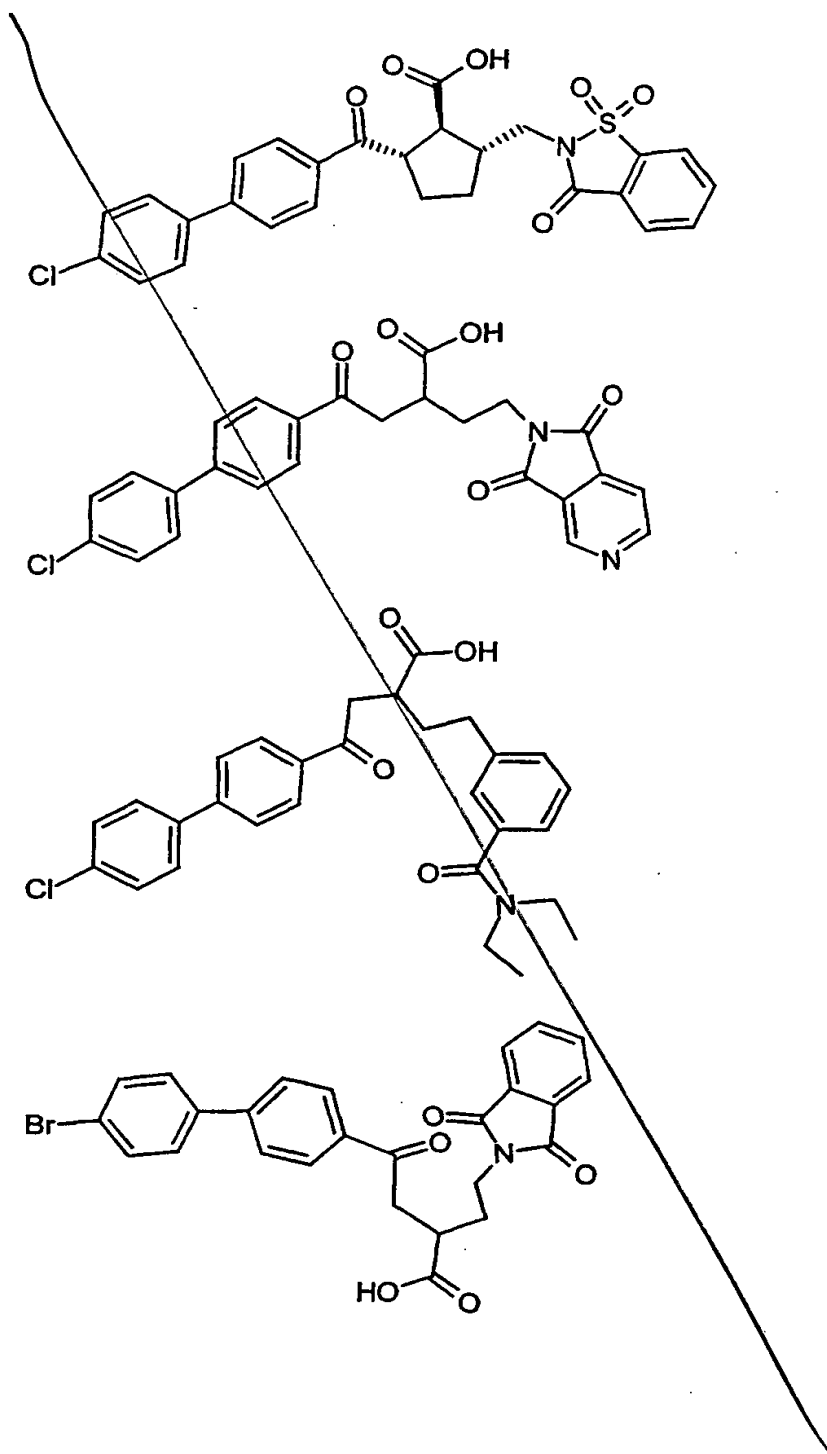
Sub  
A'

202010-09969850



Sub  
A1

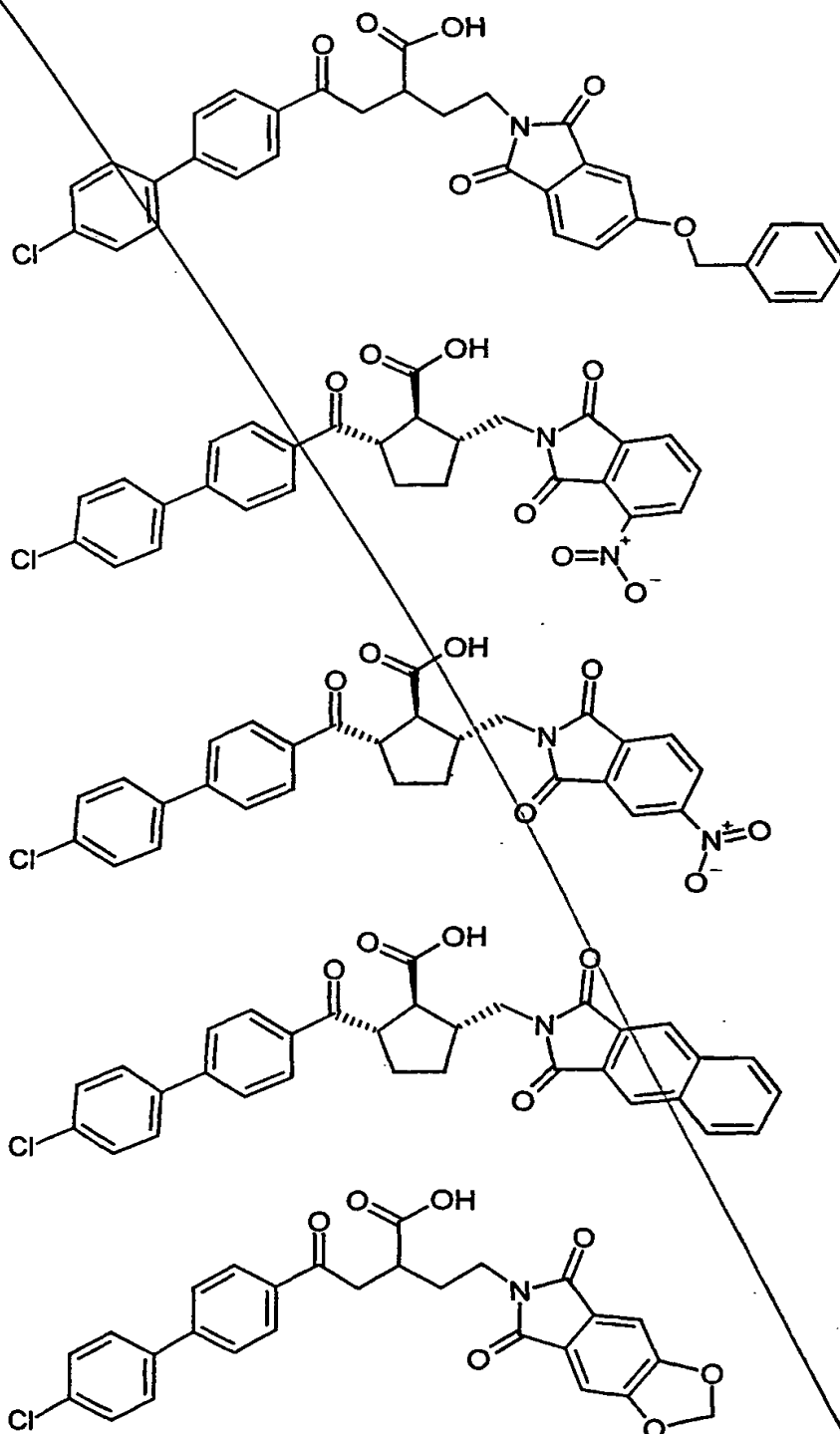
202070-89969860



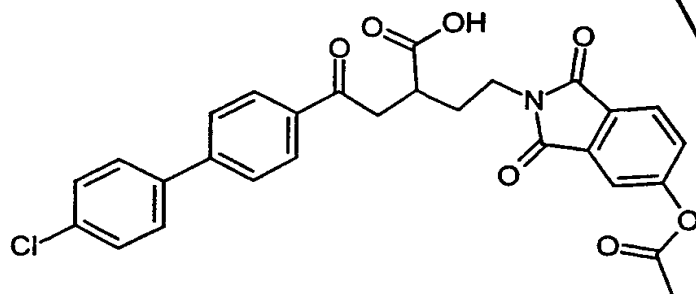
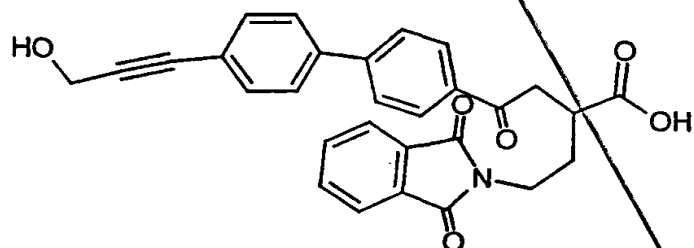
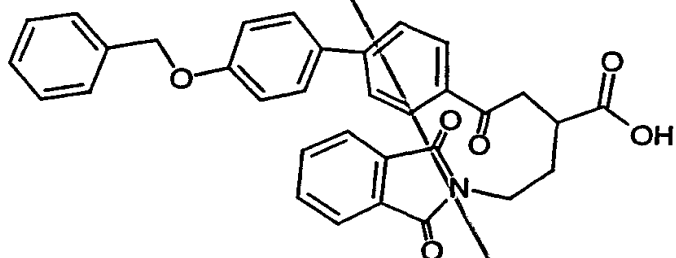
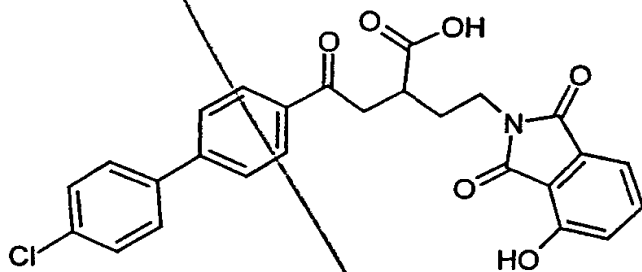
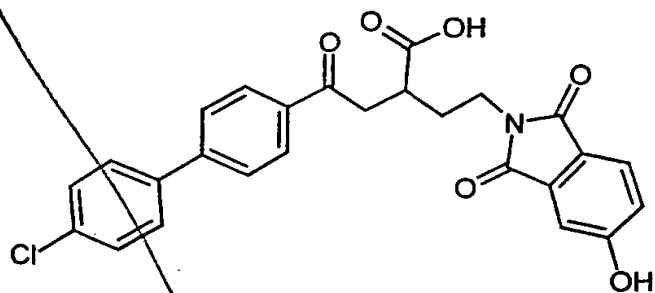
- 129 -

Sub  
A'

09869860

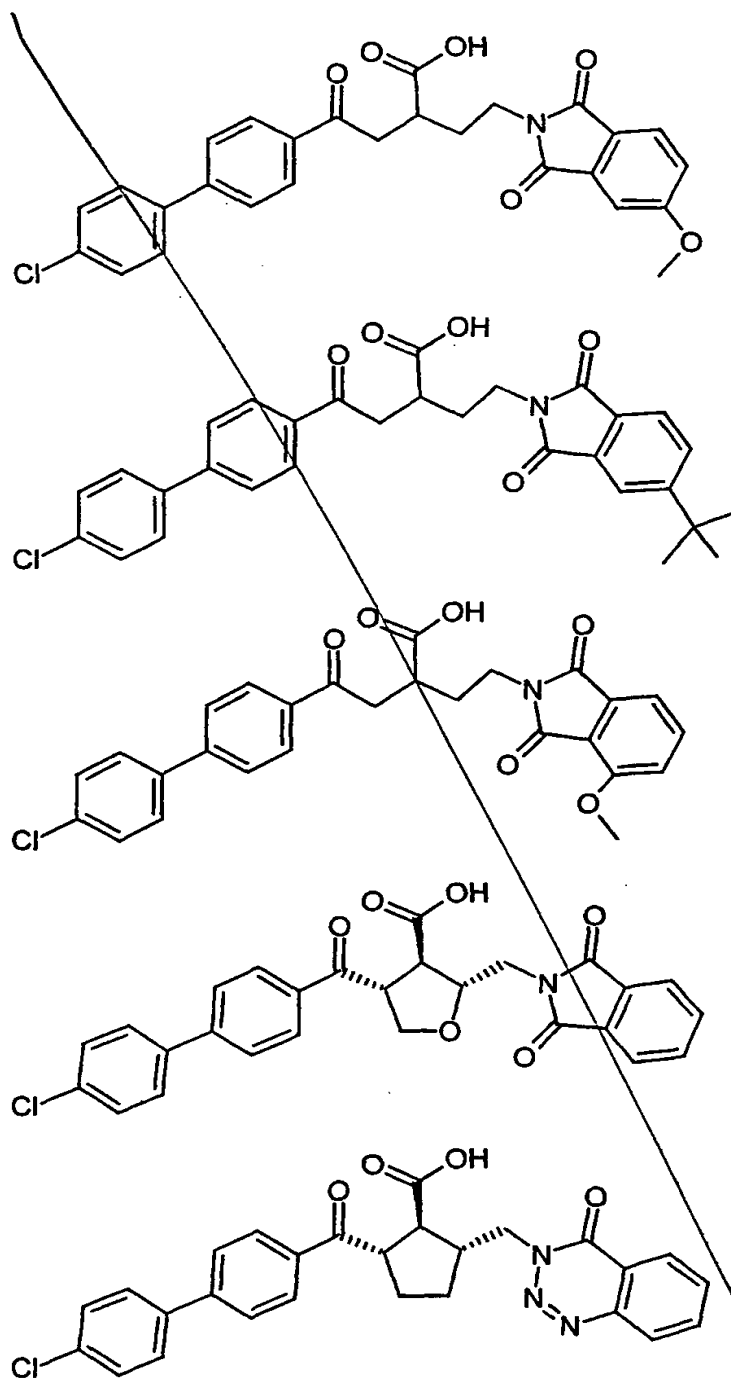


- 130 -



Sub  
A'

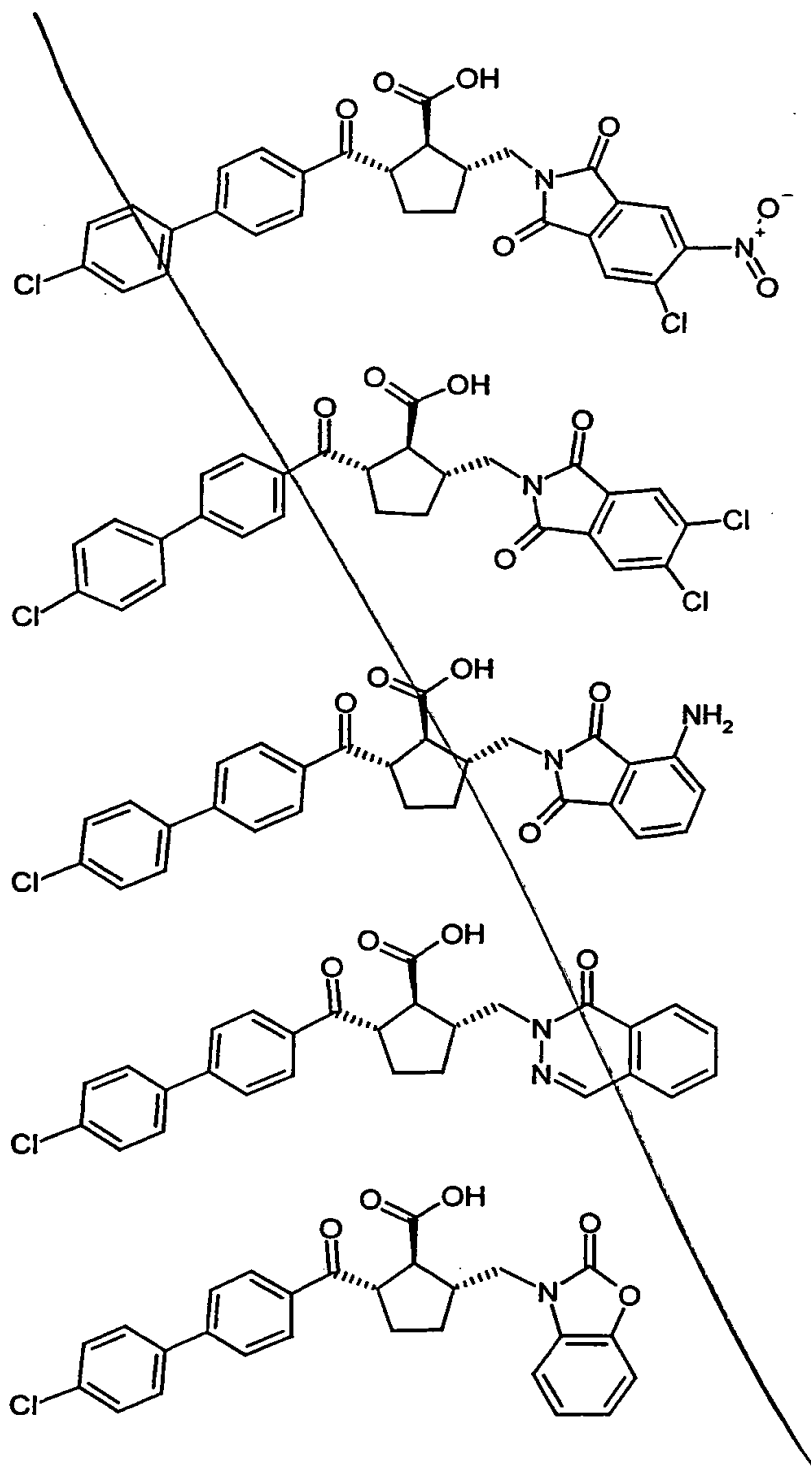
202070-89969860



- 132 -

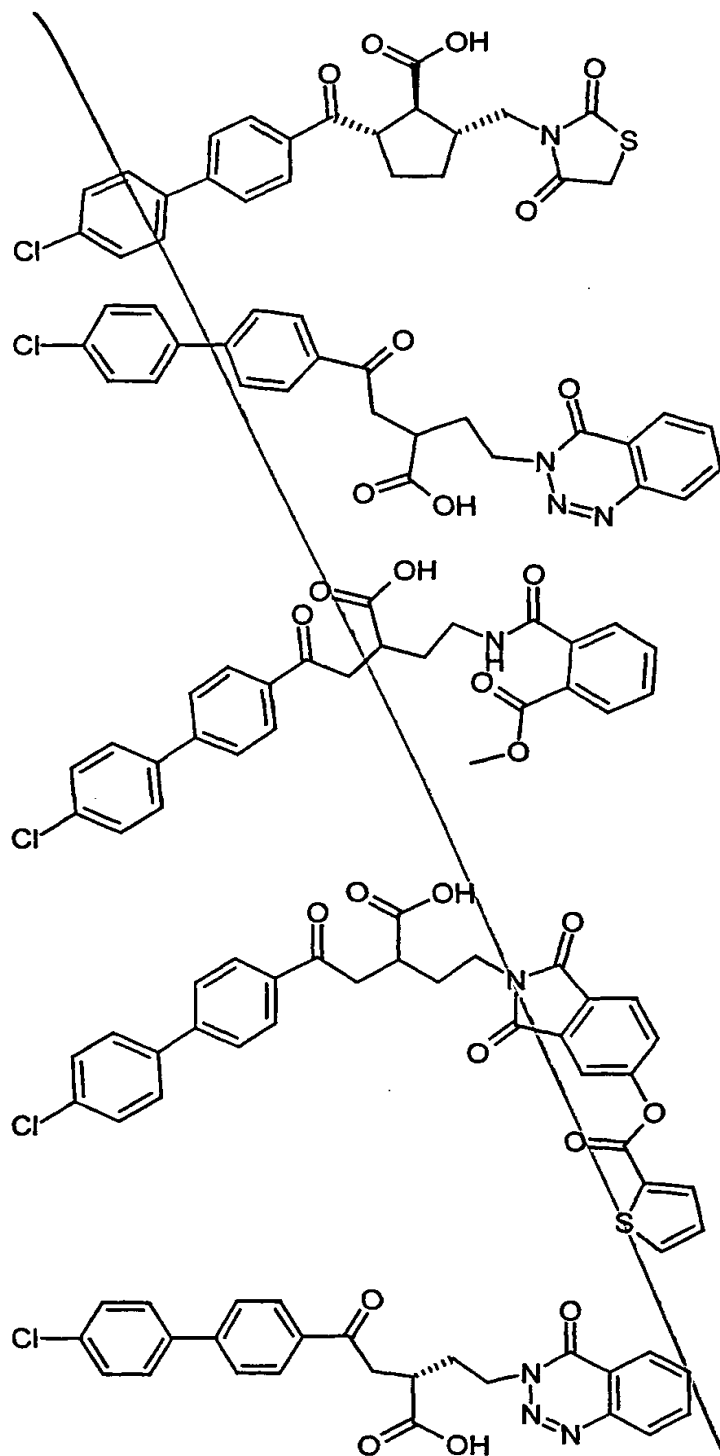
Sub  
A1

09869668.010203



Sub  
A'

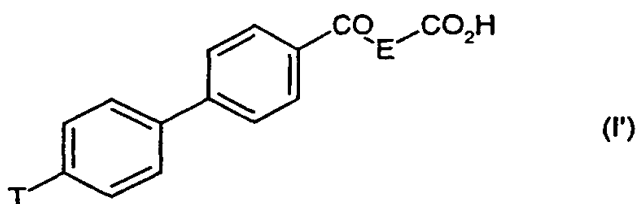
202070-89969860



for the manufacturing of drugs for the treatment and prevention of respiratory diseases.



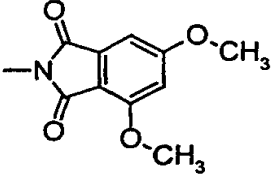
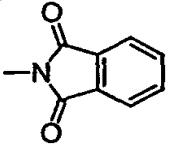
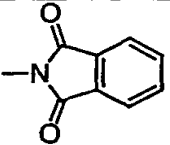
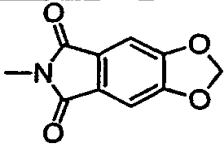
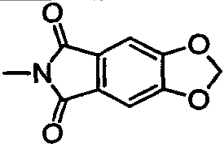
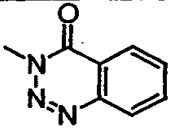
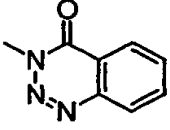
## 7. Compounds of the general formula (I')



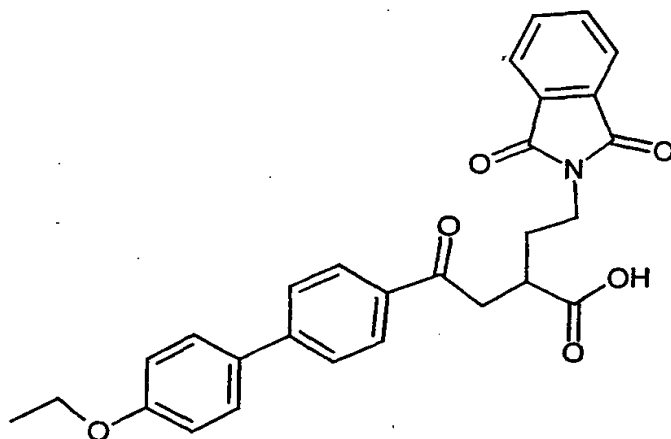
5.

wherein CO-E-CO<sub>2</sub>H represents a 3-carboxyl-5-R<sup>7</sup>-pentan-1-on-1-yl- residue and the substituents T and R<sup>7</sup> have the meaning indicated in the following table:

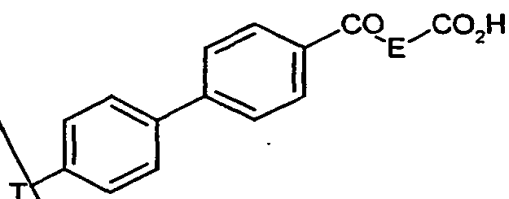
T	R <sup>7</sup>	racemate, (+)- or (-)- enantiomer	
OEt		(+)	;
OEt		(-)	;
OAc		rac	;
OH		rac	;

T	R <sup>7</sup>	racemate, (+)- or (-)- enantiomer	
Cl		rac	;
Br		(+)	;
Br		(-)	;
Cl		(+)	;
Cl		(-)	;
CN		rac	or
OCF <sub>3</sub>		rac	.

8. A compound (+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid



9. Use of compounds of the general formula (I')



(I')

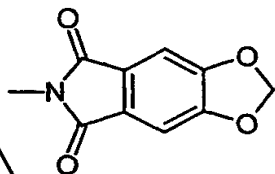
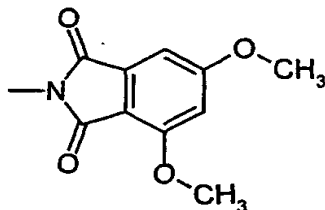
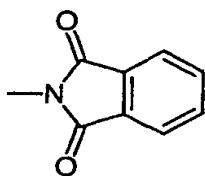
wherein

T is (C<sub>1</sub>-C<sub>4</sub>)-alkoxy, chloride, bromide, fluoride, acetoxy, hydroxy, cyano, trifluoromethyl or trifluoromethoxy,

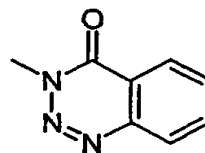
CO-E-CO<sub>2</sub>H represents a 3-carboxyl-5-R<sup>7</sup>-pentan-1-on-1-yl- or a 2-carboxyl-3-(R<sup>7</sup>-methyl)-cyclopentan-1-yl)carbonyl-residue, and

R<sup>7</sup> represents a group of the formula

- 137 -



or

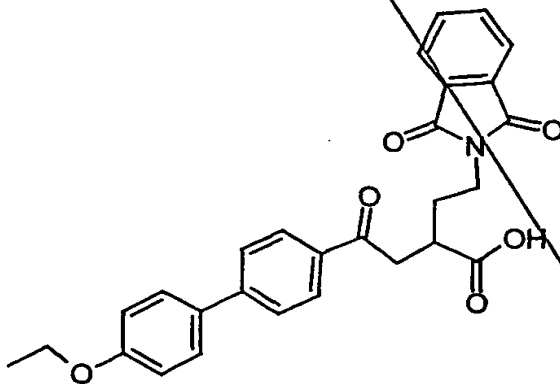


and their salts, for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

5

#### 10. Use of the compound

(+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid,



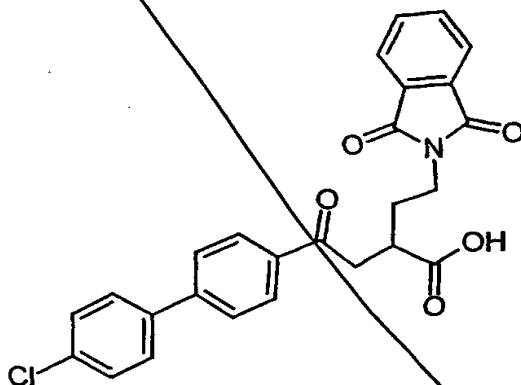
10

for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

Sub  
A2

09869668.010202

11. Use of the compound (+)-4-(4'-chloro[1,1'-biphenyl]-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid



for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

12. The use of a compound according to any one of claims 1 to 6 or 9 to 11 in the manufacture of a medicament for the treatment of a condition mediated by MMP-2, MMP-3, MMP-9, MMP-12 and/or MMP-13.

13. A method of treating or preventing a condition mediated by MMP-2, MMP-3, MMP-9, MMP-12 and/or MMP-13, which comprises administration of an effective amount of a substance according to any one of claims 1 to 6 or 9 to 11.

14. Use of a compound according to any one of claims 1 to 6 or 9 to 11 for the treatment and prevention of asthma; chronic obstructive pulmonary diseases including chronic bronchitis and emphysema; cystic fibrosis; bronchiectasis; adult respiratory distress syndrome (ARDS); allergic respiratory disease including allergic rhinitis; diseases linked to  $TNF_{\alpha}$  production including acute pulmonary fibrotic diseases, pulmonary sarcoidosis, silicosis, coal worker's

Sub  
A3

pneumoconiosis, alveolar injury in mammals, such as human, a farm animal or a domestic pet.

5

15. Use of a composition having matrix metalloprotease inhibitory activity, comprising a compound of any one of claims 1 to 12 and a pharmaceutically acceptable carrier for the manufacturing of drugs for the treatment and prevention of respiratory diseases.

Sub  
A4<sup>10</sup>

16. Composition containing compounds according to Claim 7 or 8.
17. Composition according to Claim 16 for the treatment and prevention of acute and chronic inflammatory processes.

00000000.010202